

## Recurrence of hepatocellular carcinoma presenting as an asymptomatic appendiceal tumor: report of a case

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**Abstract** This report presents the case of a 66-year-old male with appendicular metastasis from hepatocellular carcinoma. He had a clinical history of right lobectomy of the liver after the diagnosis of hepatocellular carcinoma 3 years prior, and was admitted because of an asymptomatic appendiceal tumor detected by computed tomography. The appendiceal tumor was preoperatively suspected to be a recurrence of hepatocellular carcinoma, because of the patient's elevated level of serum  $\alpha$ -fetoprotein and protein induced by vitamin K absence or antagonist II, and based on the magnetic resonance imaging findings. An appendectomy was thus performed, and the histopathological findings confirmed the diagnosis of a metastatic tumor from hepatocellular carcinoma. Appendicular metastasis is extremely rare. This is only the second case of a metastatic appendiceal tumor from hepatocellular carcinoma reported in the English literature.

**Keywords** Hepatocellular carcinoma · Metastasis · Appendiceal tumor

### Introduction

Metastatic appendiceal tumors are very rare. The major primary lesions in such cases are usually in the breast, lung, stomach, and ovary [1].

This report describes the second case of a metastatic appendiceal tumor from hepatocellular carcinoma (HCC) described in the English literature. This is the first case of a solitary and metachronous metastasis to the appendix from HCC.

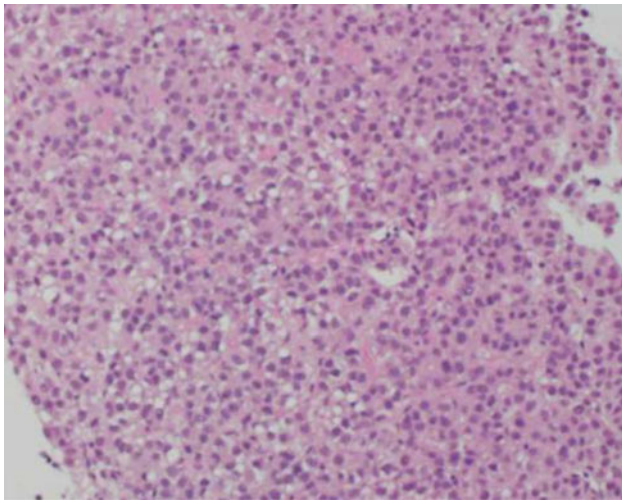
### Case report

A 66-year-old male was admitted because of an asymptomatic appendiceal tumor detected by computed tomography (CT). He had a clinical history of lung adenocarcinoma (pT1N0M0, Stage IA) that was removed by superior lobectomy of the left lung 5 years earlier, and HCC (pT2N0M0, Stage II) that was removed by right lobectomy of the liver 2 years later. The tumor of the liver was confirmed to be HCC based on the biopsy findings, and it was hypovascular, a typical feature of HCC (Fig. 1). Most of the hepatocellular carcinoma cells were necrotic due to preoperative transarterial embolization.

A physical examination revealed no tenderness in his abdomen, and no mass was palpable. His laboratory findings showed a normal white blood cell count and C-reactive protein level, and an elevated level of serum  $\alpha$ -fetoprotein (AFP; 37 ng/ml; normal, <6.5) and protein induced by vitamin K absence or antagonist II (PIVKA-II; 209 mAU/ml; normal, <40). CT revealed a distended appendix (8 cm by 3.5 cm) with good contrast enhancement (Fig. 2). The surrounding fat tissue showed no inflammatory changes. There were no enlarged lymph nodes. A colonoscopic examination revealed normal mucosa, and mucosal elevation was suspected to be due to neoplastic pressure in the appendicular orifice. Ultrasonography revealed a distended appendix as a hypoechoic mass. A dynamic-enhanced magnetic resonance imaging

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**Fig. 1** The tumor cells showed hepatoid proliferation in a trabecular or pseudo-canalicular pattern (H&E,  $\times 50$ )



**Fig. 2** Computed tomography revealed a distended appendix (8 cm by 3.5 cm) with good contrast enhancement

(MRI) examination revealed a low-intensity mass on a T1-weighted image (Fig. 3a) and a high-intensity mass on a T2-weighted image (Fig. 3b), which was well enhanced on the early-arterial phase (Fig. 3c), and washed out on the late-arterial phase (Fig. 3d). Positron emission tomography (PET) with  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) revealed an intense area of increased uptake ( $\text{SUV}_{\text{max}}$ : 3.4) in the region that corresponded to the enlarged appendix. There were no other areas of an increased uptake.

The differential diagnosis was a metastasis from lung cancer, a primary appendiceal tumor, such as mucinous adenoma, mucinous adenocarcinoma, non-mucinous adenocarcinoma, lymphoma, carcinoid tumor, or hepatoid carcinoma. However, the appendiceal tumor was suspected to be a recurrence of HCC, because of the elevated level of serum AFP and PIVKA-II, based on the MRI findings, and the clinical history of HCC.

Laparotomy revealed the appendix to measure 9.5 cm by 4.0 cm in size, and did not adhere to the surrounding tissues. There was no invasion of the serosa caused by the tumor, and no swelling lymph nodes were noted. Therefore, an appendectomy was performed (Fig. 4a). The lumen of the specimen was filled with tumor cells (Fig. 4b).

Microscopic examination of the surgical specimen showed that the tumor growth was mainly in the submucosa, extending to the lumen of the appendix. The tumor cells showed hepatoid proliferation in a trabecular or pseudo-canalicular pattern with hematoxylin and eosin staining (Fig. 5a, b). Immunohistochemical staining showed that the tumor cells were positive for hepatocyte paraffin 1 (Fig. 5c), but negative for  $\alpha$ -fetoprotein (Fig. 5d), cytokeratin 7, cytokeratin 19, cytokeratin 20, CD56, synaptophysin, chromogranin A, and neuron-specific enolase (data not shown). The tumor was pathologically confirmed to be HCC metastasis. The patient is still alive 20 months after the appendectomy, despite developing an intrahepatic recurrence of HCC.

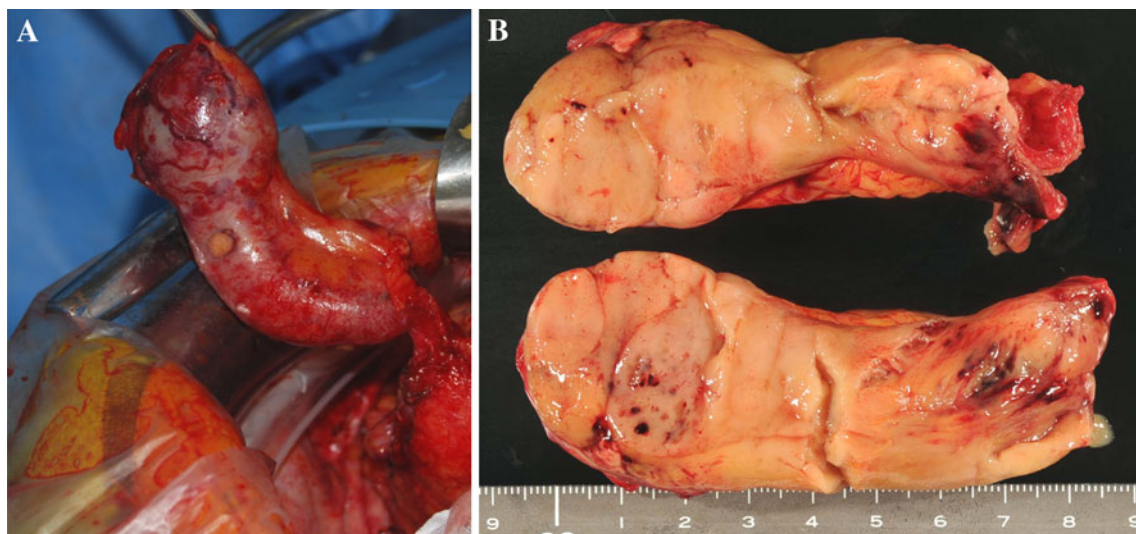
## Discussion

Malignant tumors of the appendix are uncommon [2]. An epidemiological survey performed by McCusker et al. [3] demonstrated that the age-adjusted incidence of cancer of the appendix was 0.12 per 1,000,000 cases per year. Tumors account for 0.2–0.3 % of appendectomy specimens. Moreover, metastatic carcinoma of the appendix is extremely rare. Collins [4] did not report any cases of metastasis to the appendix in his analysis of 71,000 appendix specimens. Similarly, a review by Blair et al. [5] showed no metastatic tumors of the appendix in 2,216 appendectomy specimens. Berge and Lundberg [6] documented only 7 cases in 16,294 autopsies.

Extrahepatic metastasis of HCC is also uncommon. The lungs, abdominal lymph nodes, and bones are the most common metastatic sites of HCC. The involvement of the gastrointestinal (GI) tract from HCC occurs in just 0.5–2 % of cases. The major mode of metastasis to the GI tract is direct invasion to the contiguous GI tract by a bulky tumor mass. HCC rarely spreads hematogenously to the distant GI tract [7]. The first reported case of metastasis to the appendix from a HCC showed multiple small nodules in the omentum and peritoneum. Their microscopic examination showed that the tumor cells had infiltrated to the mucosa from the serosa. Therefore, the authors suggested that an unrecognized rupture of the HCC in the liver had occurred, followed by implantation of the HCC cells onto the mesoappendix, and subsequent invasion of the appendiceal wall. However, preoperative PET showed no area of an increased uptake other than the appendix, no invasion of



**Fig. 3** Dynamic-enhanced magnetic resonance imaging revealed a low-intensity mass on the T1-weighted image (**a**), and a high-intensity mass on the T2-weighted image (**b**), which was well enhanced during the early-arterial phase (**c**), then washed out during the late-arterial phase (**d**)



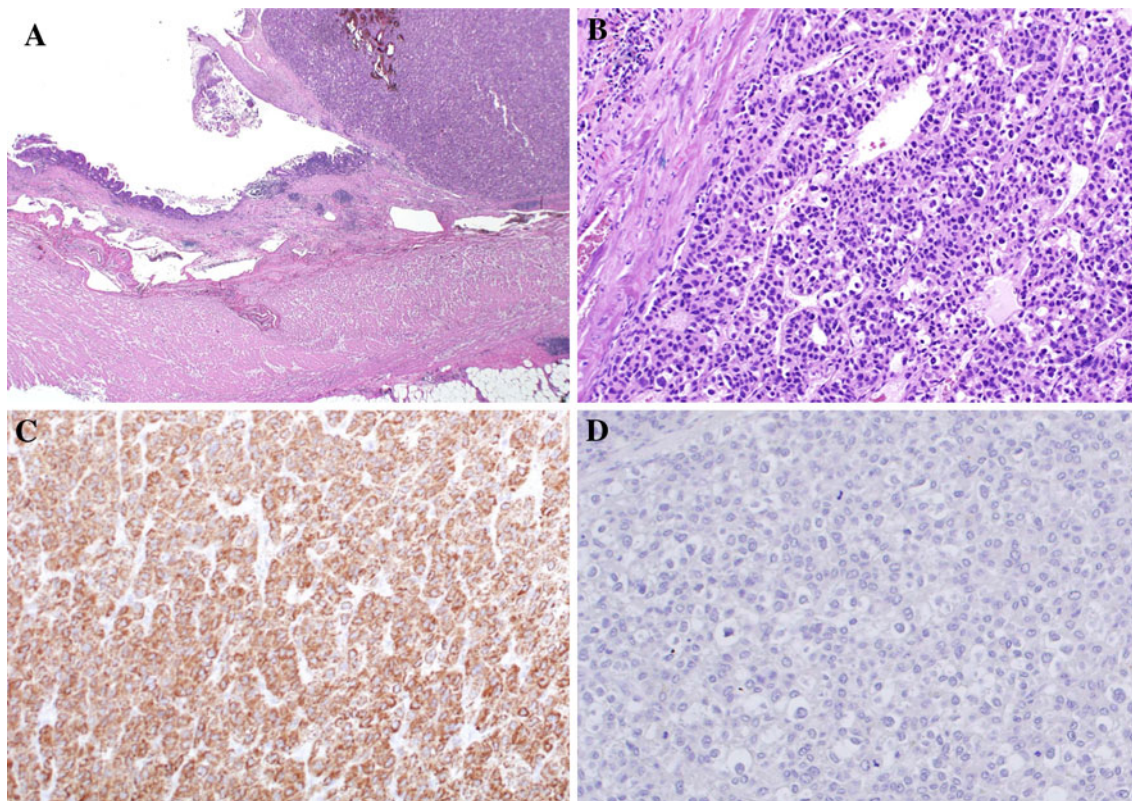
**Fig. 4** The surgical view (**a**). The appendix was 9.5 cm by 4.0 cm in size. A macroscopic view of the resected specimen (**b**). The lumen of the specimen was filled with tumor cells

the serosa of the appendix, and no nodules suspected to be dissemination into the peritoneal cavity were seen at laparotomy in the current case. Moreover, the tumor grew mainly in the submucosa, extending into the lumen of the appendix. Therefore, the mechanism of metastasis to the

appendix was thought to be by hematogenous spread, and thus the mechanism of metastasis is different between the first report and the current case.

Although a metastatic tumor of the appendix is extremely rare, patients frequently have symptoms of acute





**Fig. 5** The microscopic examination of the specimen. Tumor growth was mainly observed in the submucosa, extending to the lumen of the appendix (**a** H&E,  $\times 10$ ). Similar to Fig. 1, the tumor cells showed hepatoid proliferation in a trabecular or pseudo-canalicular pattern

(**b** H&E,  $\times 50$ ). Immunohistochemical staining studies were positive for hepatocyte paraffin 1 (**c**  $\times 50$ ), but negative for  $\alpha$ -fetoprotein (**d**  $\times 100$ )

appendicitis [8]. Cerame [9] reviewed 316 case reports of adenocarcinoma of the appendix. He demonstrated that a primary tumor is rarely suspected at the time of initial surgery, as 68 % of the patients present with signs and symptoms of inflammatory disease of the appendix. He also demonstrated that the appendiceal wall is perforated by the tumor in 55 % of patients. The appendiceal lumen was occluded by tumor cells in the current case, but the appendiceal tumor was detected with no symptoms of perforation. Furthermore, the appendiceal tumor was suspected to be a metastatic tumor from HCC prior to surgery. The MRI findings of the appendiceal tumor were well enhanced during the early-arterial phase and washed out during the late-arterial phase, similar to primary HCC. These findings were particularly useful for the diagnosis of metastasis from HCC.

However, it was difficult to preoperatively differentiate hepatoid carcinoma from hepatocellular carcinoma. Hepatoid carcinoma has also been reported to be difficult to differentiate from hepatocellular carcinoma by cytology, and the absence of any primary identifiable liver disease is crucial evidence for the diagnosis of hepatoid carcinoma [10]. Immunohistochemical staining was conducted based

on the findings of Hsu et al. [10], and Liu et al. [11]. Liu et al. reported that hepatoid and adenocarcinomatous components demonstrate the presence of cytokeratin (CK)  $18^+/CK\ 19^+$ , whereas both normal and neoplastic hepatocytes demonstrate  $CK\ 18^+/CK\ 19^-$ . The current specimens were stained with CK 19 antibodies to distinguish HCC from hepatoid carcinoma. The tumor cells were negative for CK19, and thereby were accurately diagnosed as HCC of the appendix.

In conclusion, appendiceal metastasis from HCC is uncommon, and HCC rarely spreads hematogenously to the appendix. This report presented the first case of solitary and metachronous metastasis to the appendix from HCC.

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